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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,324	10/07/2005	Hans Loibner	4518-0111PUS1	8937

2292 7590 03/24/2010

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EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
03/24/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/552,324	LOIBNER ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 34-39 are all the pending claims for this application.

2. Claims 1-10 and 12-33 were cancelled, Claim 34 was amended and new Claims 35-39 were added in the Response of 1/19/10.

3. Claims 34-39 are all the pending claims under examination.

4. Applicants amendments to the claims have necessitated new grounds for rejection. This Office Action is final.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, first paragraph

Enablement

5. The rejection of Claims 1-3, 5, 9, 12, 13, and 29-32 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for introducing any fragment of the constant region from an IgG2 antibody into the constant region of any IgG1 antibody in order to obtain a constant region comprising any hamster or primate glycosylation and being immunogenic in any primate is withdrawn and moot.

Applicants cancelled the claims in the Response of 1/19/10.

Written Description

6. The rejection of Claims 1-3, 5, 9, 12, 13, and 29-32 under 35 U.S.C. 112, first paragraph, because the claims encompass antibodies comprising any IgG2a subtype region from the constant domain cloned into the constant region an IgG1 antibody where the IgG2a comprises a hamster or primate glycosylation and the resultant

recombinant antibody is designed for immunizing primates is withdrawn and moot.

Applicants cancelled the claims in the Response of 1/19/10.

Claim Rejections - 35 USC § 103

7. The rejection of Claim 34 under 35 U.S.C. 103(a) as being unpatentable over Debe et al. (U.S.A.N. 09/791,537; filed 2/22/01) is withdrawn.

Applicants amended the claim in the Response of 1/19/10 to introduce the limitation that the antibody fragment further comprises "at least a part of the murine IgG2a subtype amino acid sequence" which is neither taught nor suggested by Debe.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

8. Claims 34-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims encompass an antibody fragment of SEQ ID NO: 2, 3, 4 or 5 and further comprising any region including the full length IgG2a subtype attached to the N- or C-terminal of the antibody fragment and any hamster or primate glycosylation where the resultant recombinant antibody is immunogenic. Additionally, according to the definition in the specification an "immunogenic antibody" "may have immunogenicity by its specificity or by its structure. The immunogenic antibody can induce immunogenicity also when being denatured or when conjugated to certain structures or carriers" (p. 8, ¶6)."

Under the Written Description Guidelines (66 FR 1099 (Jan. 5, 2001); 1242 O.G. 168 (Jan. 30, 2001) revised training materials Mar 25, 2008), the claimed invention must meet the following criteria as set forth.

a) Actual reduction to practice: The specification makes a general disclosure for anti-idiotypic antibodies against Lewis-Y (pp. 5, 12, 13, 14 and 36), Sialyl-Tn (p. 12) or Globo H (p. 12) carbohydrate antigens. The specification discloses an anti-idiotypic antibody for the Lewis-Y antigen in Example 8 where the recombinant IgG2a Le-Y antibody is an IgG2a hybrid designed for primate vaccination, which combines an anti-idiotyic Lewis-Y mimicking herpervariable region and the highly immunogenic mouse IgG2a constant regions as shown in Figure 4. The immunogenicity is reported to be improved over the parent antibody, IGN301 wherein the anti-idiotypic antibody produces a strong IgG response against Lewis-Y expressing epithelial cancer cells. The antibody is expressed in HEK293 cells, transformed human embryonic kidney cell cultures so would result in primate glycosylation.

It is not well established in the art that an antibody encompassed by the claims is amenable to the extent and degree of the modifications to the Fc or constant domain that would allow proper folding and assembly of the antibody, and the specification is not any more enabling for producing a functional, immunogenic antibody that meets all of the claim limitations.

b) Disclosure of drawings or structural chemical formulas: the specification and drawings do not show that applicant was in possession of the genus of immunogenic antibodies comprising containing just any portion an IgG2a constant region and where the constant region IgG1/IgG2a hybrid comprises any extent and amount of glycosylation.

c) Sufficient relevant identifying characteristics: the specification does not identify 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between structure and function for the genus of immunogenic antibody.

d) Method of making the claimed invention: the specification teaches making a single example of the hybrid immunogenic antibody in Figure 4 and Example 8.

e) Level of skill and knowledge in the art: the cloning of antibody DNA, construction Fc region hybrids, protein expression in CHO (hamster) and eukaryotic (primate cells) for hamster and primate glycosylation and bioassays for identifying functional regions within proteins was well established at the time of the invention.

f) Predictability in the Art: Applicants have not characterized the genus of IgG1/IgG2a hybrid antibody being hamster or primate glycosylated in the constant

region and which renders or contributes to the immunogenicity of the antibody. Applicants have not characterized the immunogenic IgG1/IgG2a hybrid antibody comprising SEQ ID NO: 2, 3, 4 and/or 5 being fused to just any region of an IgG2a and which confers immunogenicity for the antibody. The ordinary artisan could reasonably conclude that Applicants were not in possession of the claimed genus of immunogenic antibodies meeting all of the structural and functional requirements of the claims.

Enablement

9. Claims 34-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an anti-idiotypic antibody for the Lewis-Y antigen where the recombinant IgG2a Le-Y antibody is an IgG2a hybrid designed for primate vaccination, which combines an anti-idiotyic Lewis-Y mimicking herpervariable region and the highly immunogenic mouse IgG2a constant regions as shown in Figure 4, does not reasonably provide enablement for introducing any fragment of the constant region from an IgG2 antibody into the constant region of any IgG1 antibody of SEQ ID NO: 2, 3, 4 and/or 5 in order to obtain a constant region comprising any hamster or primate glycosylation and being immunogenic in any primate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir.1988). They include the nature of the invention, the state of the prior art, the relative skill of those in

the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention

The claims encompass antibodies comprising an antibody portion of SEQ ID NO: 2, 3, 4 and/or 5 and just any IgG2a subtype region from the constant domain cloned into the constant region an IgG1 antibody where the IgG2a comprises a hamster or primate glycosylation and the resultant recombinant antibody is designed for immunizing primates.

Disclosure in the Specification

The specification makes a general disclosure for anti-idiotypic antibodies against Lewis-Y (pp. 5, 12, 13, 14 and 36), Sialyl-Tn (p. 12) or Globo H (p. 12) carbohydrate antigens. The specification discloses an anti-idiotypic antibody for the Lewis-Y antigen in Example 8 where the recombinant IgG2a Le-Y antibody is an IgG2a hybrid designed for primate vaccination, which combines an anti-idiotyic Lewis-Y mimicking herpervariable region and the highly immunogenic mouse IgG2a constant regions as shown in Figure 4. The immunogenicity is reported to be improved over the parent antibody, IGN301 wherein the anti-idiotypic antibody produces a strong IgG response against Lewis-Y expressing epithelial cancer cells. The antibody is expressed in HEK293 cells, transformed human embryonic kidney cell cultures so would result in primate glycosylation.

It is not well established in the art that an antibody encompassed by the claims is amenable to the extent and degree of the modifications to the Fc or constant domain that would allow proper folding and assembly of the antibody, and the specification is not any more enabling for producing a functional, immunogenic antibody that meets all of the claim limitations.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed immunogenic recombinant antibody fragment in a manner reasonably correlated with the scope of the claims broadly including any region of the murine IgG2s subtype and any number and kind of glycosylation to the antibody. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

Prior Art Status: glycosylation of antibodies is unpredictable, dependent on the cell type and can affect antibody function.

It is known that not all cells glycosylate proteins in the same manner. As evidenced by Wright et al (Springer Semin Immunopathology ,15 :259-273 (1993); cited in the PTO 892 form 9/2/08), while N-linked glycosylation is a wide spread post translational modification, occurring among mammalian, yeast, insect and plant cells,

"the processing steps in the Golgi apparatus vary among cell types". (Page 259, second paragraph). Wright documents that plant cells use xylose, mammalian cells use sialic acid, and yeast add many more mannose monomers than mammalian cells. Also insect cells do not appear to process the carbohydrates beyond the Man3 GLC Nac2 step. Accordingly, one skilled in the art would reasonably conclude that the tertiary structure of glycosylated antibodies, if actually glycosylated, which are encompassed by the broadly written claims would differ, based upon the teachings of Wright et al.

Further, Wright et al specifically teach that "the position of the carbohydrate addition appears to influence the structure of the added carbohydrate" (page 269, first full paragraph) and that "glycosylation can induce structural abnormalities in the light chain that lead to tissue deposition" (page 266-267, bridging paragraph). Finally, Wright et al teach that the sugars may fill “pockets" within the immunoglobulin , thus one of ordinary skill in the art would reasonably conclude that addition of carbohydrates to an antibody would alter the tertiary structure as evidenced from Delente (Trends in Biotechnology 3, letters to editor, No.9, (1985); cited in the PTO 892 form 9/2/08) which teaches each glycosylated protein must be evaluated individually to determine the importance of glycosylation to its function and stability. Thus Wright et al teach the unpredictability of adding a glycosylation site to an antibody molecule, specifically that some additions result in protein aggregation; that the position of the addition is important for determining whether the glycosylation site is in fact recognized by the cell; and once glycosylated, whether the antibody is more or less stable and binds antigen like the unaltered form. One skilled in the art would also reasonably conclude from

Wright et al that glycosylation in the CH1 or constant K (CK) region could have similar structural effects as those in the light chain mentioned above.

As evidenced by Olden et al (Biochem et Biophys Acta 650:209-232 (1982); cited in the PTO 892 form 9/2/08), carbohydrate structures are a form of sorting signals used by the cells and that O-linked glycosylation differ from N-linked glycosylation due to the sugars which are added to each type during protein processing. O-linked carbohydrates use gaINAC while N-linked carbohydrates use GlcNAC (see page 225, second column, first paragraph). Olden teaches that O-linked carbohydrates differ in tertiary structure from N-linked carbohydrates and therefore, one skilled in the art would reasonably conclude that antibodies possessing O-linked sugars would also differ in their tertiary structure from those antibodies expressing N-linked sugars.

Moreover, while the N-linked carbohydrate addition site is specifically the sequence "ASP-X-SER/THR, where X may stand for any amino acid, the O-linked addition site is less defined as only a serine or a threonine residue. Carbohydrate moieties are not attached to all lumenal serine or threonine residues and it would be unpredictable to determine at which lumenal positions a serine or a threonine could be placed within the antibody molecule so that the serine or threonine would be glycosylated. Once glycosylated, whether by the N-linked or O-linked mechanism, it would require undue experimentation to determine whether the antibody expression, stability, tertiary structure or affinity had been affected.

Since the state of the art of protein modification suggests that the effects of sequence alterations are unpredictable, and furthermore, as evidenced by Wright et al,

Delente, and Olden et al concerning the unpredictability of adding carbohydrates to antibodies and since the specification provides inadequate guidance as to which constant domain changes would result in hamster or primate glycosylation and a functional antibody, wherein the glycosylation site is actually used, and the antibody stability/function is not reduced, undue experimentation would be required to determine which IgG2 constant domain regions would result in the hamster- or primate-glycosylated antibody molecule that could still be bind its antigen and would be used to immunize primates.

Prior Art Status: Modifications to the Heavy Chain Constant Regions are Unpredictable

The claims encompass antibodies comprising modified constant regions and are not limited to the domain substitutions. The claims do not specify whether the hinge, CH1, CH2 or CH3 domains are substituted or where the substitutions would take place. It is well accepted in the art that the constant region contributes to flexibility, half-life and the effector functions of an antibody.

Salfeld (Nature Biotech. 25(12): 1369-1372 (2007); cited in the PTO 892 form 9/2/08) describes some of the properties for the IgG isotype constant regions in Table 1 and suggests that the constant region can be modified based on the intended effector functions but that results can vary depending on which domain and how the domain is mutagenized (p. 1371, Col. 2, ¶2-3).

The state of the art at the time the invention was made recognized that even single amino acid differences can result in drastically altered function of antibodies. For

example, Lund et al. (The Journal of Immunology 1996, 157:4963-4969); cited in the PTO 892 form 9/2/08) show that even a single amino acid replacement within the CH2 domain of IgG can alter the glycosylation profile of an antibody therefore influence its effector functions of Fc receptor binding and complement activation (see entire document, particularly Discussion on pages 4966-4968). Further, Lazar et al. (WO 03/074679); cited in the PTO 892 form 9/2/08) teach that the determinants of antibody properties, such as stability, solubility and affinity for antigen, important to its functions are overlapping; thus engineering an Fc region of an antibody may cause a loss in affinity for its antigen (see entire document, particularly page 3).

Given the extensive variation permitted by the instant claim language, the skilled artisan would not reasonably predict the combination of which IgG2 constant domain region, for example, CH1, hinge, CH2, CH3, and CH4 much less the CL have the same function as the instant claimed invention. Reasonable correlation must exist between the scope of the claims and scope to enablement set forth.

The specification does not appear to provide sufficient guidance as to which constant domains should or should not be changed to preserve any particular function. The variation permitted by the instant claim language is extensive. There does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the claimed recombinant antibody.

Therefore, in view of the lack of guidance in the specification and in view of the unpredictability in the art of glycosylation of proteins as evidenced by Wright et al, Olden et al, Delente and Lazar, and the unpredictability of glycosylation of antibodies as

evidenced by the specification, one of skill in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Conclusion

10. No claims are allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Primary Examiner, Art Unit 1643